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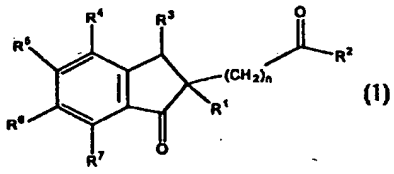
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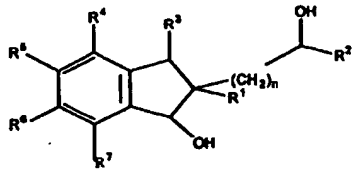
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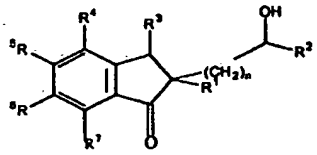
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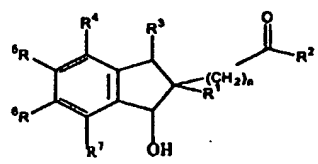
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(57) Abstract

Indane compounds of general formulae (1) to (4) and their pharmaceutical use, particularly to achieve mast cell stabilising activity and/or anti-inflammatory activity are discribed. In these formulae R^1 to R^7 may be selected from: H, halo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, cyclopentyl, alkyl carbonyl, hydro carbonyl, amino, amido, alkylamino, hydroxyamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrazone groups, indane, indene, imide groups, iminoether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitirile, heterocyclic groups containing hetero atoms selected from one or more of N, O or S, aralkyl groups, aryl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenylthiol groups, sulphonic acid groups, sulphoxide groups, sulphone groups, carboxylic acid groups of C_1 to C_{10} which may be substituted or unsubstituted, alkyl, substituted alkyl groups, acyl groups, substituted acyl groups; where R^1 and R^3 may together represent a double bond and wherein in $(CH_2)_n$, n is 0 to 8.

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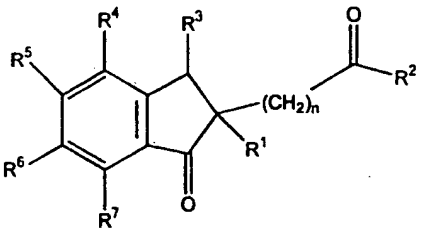
INDANE COMPOUNDS AND THEIR PHARMACEUTICAL USE

The invention relates to indane compounds, processes for their production, compositions containing them and their pharmacological use.

More particularly, the invention relates to 3-aminoindanones as anti-inflammatory agents and mast cell stabilisation agents. According to the invention, there is provided a compound of any of the formulae 1-4.



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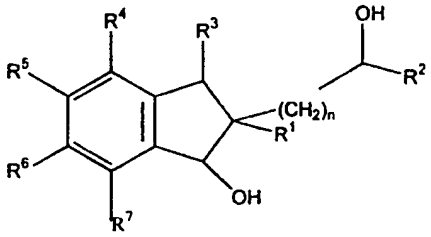

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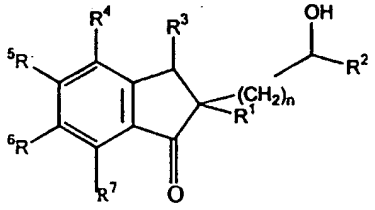

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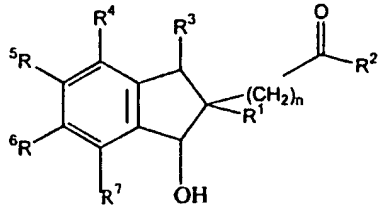

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wherein R^1 to R^7 are selected from one or more of the same or different of:-

H, halo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, cyclopentyl, alkyl carbonyl, hydro carbonyl, amino, amido, alkylamino, hydroxyamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrazone groups, indane, indene, imide groups, iminoether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitirile, heterocyclic groups containing hetero atoms selected from one or more of

N, O or S, aralkyl groups, aryl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenylthiol groups, sulphonic acid groups, sulphoxide groups, sulphone groups, carboxylic acid groups of C_1 to C_{10} which may be substituted or unsubstituted, alkyl, substituted alkyl groups, acyl groups, substituted acyl groups;

where R^1 and R^3 may together represent a double bond and wherein in $(CH_2)_n$, n is 0 to 8.

Preferred because of solubility salt formation, pharmacological activity and /or ease of production are the following subsets.

In one embodiment of the invention the compound is of the formula 2 as defined in claim 1.

In a further embodiment of the invention the compound is of the formula 3 as defined in claim 1.

In a preferred embodiment of the invention R^1 to R^7 are selected from one or more of the same or different of:-

hydroxy, alkyl of C_1 to C_{10}, aryl, substituted aryl, cyclopentyl, alkyl carbonyl, hydro carbonyl, amimo, amido, alkalamino, hydroxyamino, amide oxide groups, cyano, indane, indene, oxime, sulphonic acid groups, sulphoxide groups, sulphone groups, or heterocyclic groups containing hetero atoms selected form one or more of N, O.

Preferably R^4 to R^7 are hydrogen.

In one preferred embodiment of the invention R^1 is cyclopentyl.

In this case preferably R^1 is cyclopentyenyl.

In one preferred aspect R^1 is indane.

In another preferred aspect R^1 is indene.

In one arrangement R^2 is acyl containing 1 to 10 carbon atoms.

Alternatively, R^2 is alkyl containing 1 to 10 carbon atoms, preferably, C_1 alkyl.

In another embodiment of the invention R^2 is substituted alkyl.

In a further embodiment of the invention R^2 is aryl having 4 to 8 carbon atoms, especially C_1 aryl.

The invention especially provides the following specific compounds:

1-phenyl-2-((2'-iidenyl)-indan-2-onyl)ethan-1-one (Compound I)

1-phenyl-2-((2'-iindenyl)-indan-2-ol)ethan-1-ol (Compound II)

1-phenyl-2-((2'-iidenyl)-indan-2-ol)ethan-1-one (Compound III)

1-phenyl-2-((2'-iidenyl)-indan-2-one)ethan-1-ol (Compound IV)

1-phenyl-2-((2'-cyclopent-1-enyl)indan-1-one)ethan-1-one (Compound V)

1-((2'-iindenyl)-indan-2-one)propan-2-one (Compound VI)

1-((2'-iindenyl)-indan-2-ol)propan-2-ol (Compound VII)

1-((2'-iindenyl)-indan-2-one)propan-2-ol (Compound VIII)

1-((2'-iindenyl)-indan-2-ol)propan-2-one (Compound IX)

The compounds may be used particularly to achieve mast cell stabilising and/or anti-inflammatory activity.

The invention also provides processes for preparing the compounds as defined in claims 33 to 42.

It will be appreciated that the compounds include pharmacologically acceptable salts, esters, amides, isomers and solvates thereof.

It will also be appreciated that if the compounds have one or more chiral centres they may exist as a pair of enantiomers or as a mixture of diastereomers. This may have an effect on pharmacological properties.

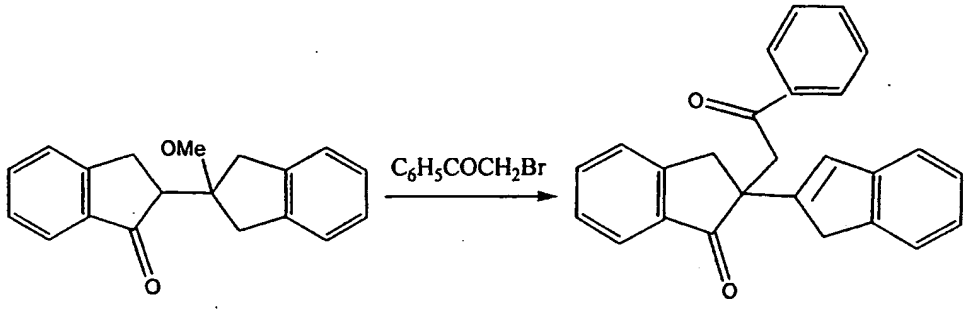
It will further be appreciated that for pharmaceutical purposes the active compounds may be formulated in any desired form using any suitable excipients and/or carriers. For example, particularly in the case for use to achieve anti-inflammatory activity the compound may be formulated in a pharmaceutical composition suitable for topical/transdermal application.

The invention will be more clearly understood from the following description thereof, given by way of example only.

Detailed Description of the Invention

In the preparation of some of the compounds of the invention are described in detail below. Some of the starting materials used are described in our earlier applications PCT/IE96/00080, PCT/IE96/00081 and PCT/IE96/00082 the contents of which are incorporated herein for reference. Other compounds within the scope of the claims can be prepared by analogy.

Example 1 Preparation of Compound I (Method A)



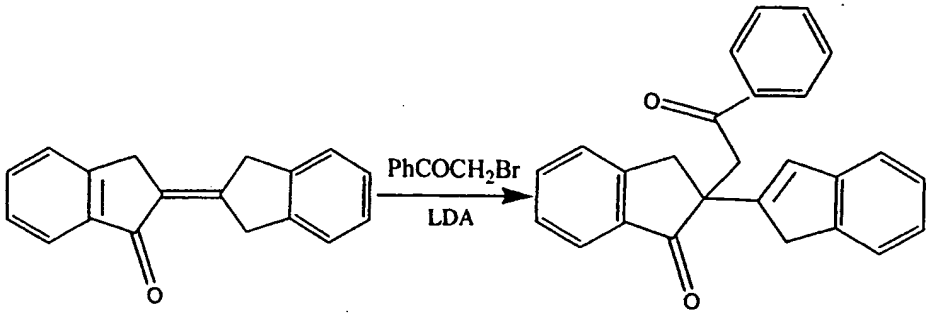
A I

Compound A (1g, 3.6 mmol) was dispersed in $^tBuOH;Et_20$ (1:9, 20ml), and to this was added phenacyl bromide (3.58g,18 mmol). To this solution, which was stirred at room temperature, potassium tert butoxide (1g) in $^tBuOH:Et_2O$ (9:1 20 ml) was added dropwise. The crude reaction mixture was extracted into ethyl acetate. The product I was isolated by column chromatography eluting with petroleum ether:ethyl acetate (9:1) (0.98g, 75%).

^1H nmr ($\delta CDCl_3$, 400 MHz) 3.35 (1H, d, J=22.5Hz,C<u>H</u> of CH_2), 3.54 (2H, t, J=14.5Hz, C<u>H</u>$_2$), 3.69 (1H,d, J=17.1 Hz, C<u>H</u> of CH_2), 3.99 (2H, q, J=18.7Hz, C<u>H</u>$_2$) 6.79 (1H,s,C=C<u>H</u>), 7.16-8.04 (13H,m, Ar-C<u>H</u>)

^{13}C nmr ($CDCl_3$, 75.47 MHz) 38.3, 39.7, 40.9 (3 x <u>C</u>H_2), 53.1 (q<u>C</u>), 120.3, 123.1, 124.2, 124.3, 125.9, 126.0, 126.4, 127.2, 127.7, 127.8, 128.1, 128.3, 128.4, 133.0 (13 x Ar-<u>C</u>H & 1 x C=<u>C</u>H), 135.3, 136.1, 142.5, 143.8, 148.2, 152.0, (5 x Ar-<u>C</u> & 1 x <u>C</u>=CH), 196.7, (CH_2<u>C</u>OC_6H_5), 204.8 (<u>C</u>O)

Example 2 Preparation of Compound I (Method B)



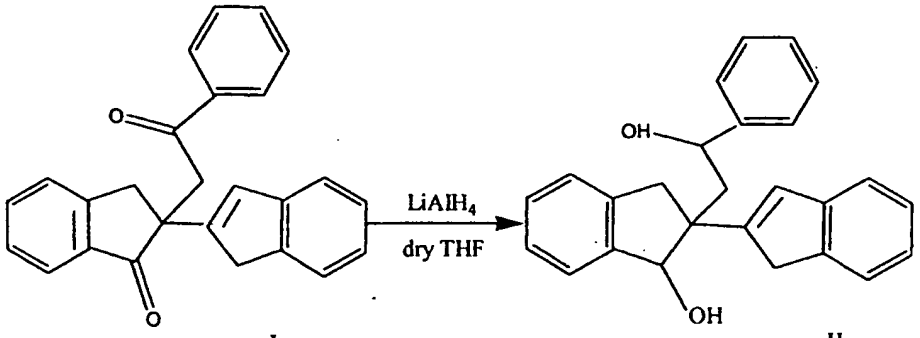
B I

Compound B (100 mg, mmol) was dispersed in THF in a clean dry 3-necked flask under nitrogen, which was cooled to -78°C. To this was added LDA (2 equivalents). After stirring for 10 minutes at -78°C, phenacyl bromide (4 equivalents) was added and the solution was allowed to warm to room temperature and stirred for 3 hours. The product I was isolated by column chromatography eluting with petroleum ether: ethyl acetate (9:1) (0.38 mg, 17%)

^{1}H nmr (δCDCl$_3$ 400 MHz) 3.35 (1H,d, J=22.5Hz, C<u>H</u> of C<u>H</u>$_2$), 3.54 (2H, t, J=14.5Hz, C<u>H</u>$_2$), 3.69 (1H, d, J=17.1Hz, C<u>H</u> of C<u>H</u>$_2$), 3.99 (2H,q, J=18.7Hz, C<u>H</u>$_2$), 6.79 (1H, s, C=C<u>H</u>), 7.16-8.04 (13H,m Ar-C<u>H</u>)

^{13}C nmr (CDCl$_3$, 75.47 MHz) 38.3, 39.7, 40.9 (3x <u>C</u>H$_2$), 53.1(q<u>C</u>), 120.3, 123.1, 124.2, 124.3, 125.9, 126.0, 126.4, 127.2, 127.7, 127.8, 128.1, 128.3, 128.4, 133.0 (13 x Ar-<u>C</u>H & 1 x C=<u>C</u>H), 135.3, 136.1, 142.5, 143.8, 148.2, 152.0 (5 x Ar-<u>C</u> & 1 x <u>C</u>=CH), 196.7 (CH$_2$<u>C</u>OC$_6$H$_5$), 204.8 (<u>C</u>O)

Example 3 Preparation of Compound II



I II

Compound I (300mg, 0.8 mmol) was dissolved in clean dry THF (10ml) and to this was added lithium aluminium hydride (300mg, 8 mmol). The crude product was extracted into ethyl acetate. The product II was obtained as a mixture of diastereomers by column chromatography eluting with petroleum ether:ethyl acetate (9:2) (0.175g, 58%)

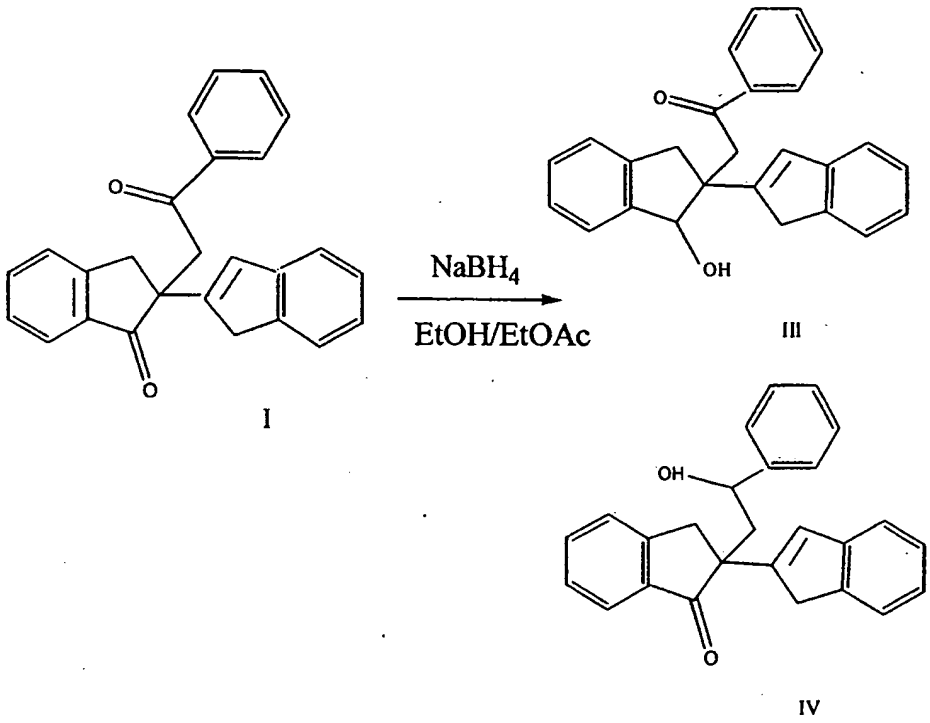
Low resolution mass Spectrum

$C_{26}H_{24}O_2$ require M^+368, Found M^+368

^{1}H nmr (δCDCl$_3$, 400 MHz) 1.97 (1H, bs, CHOHCH$_2$), 2.09 (1H, bs, CHOH), 2.13 - 2.36 (2H, m, CH$_2$), 3.12 (1H, d, J=22.6Hz, CH of CH$_2$), 3.46 – 3.52 (2H, m, CH$_2$), 3.55 (1H, d, J=23.2Hz, CH of CH$_2$), 4.77 (1H, m, CHOHCH$_2$), 4.96 (1H, s, CHOH), 6.79 (1H, s, C=CH), 7.15 – 7.41 (13H, m, Ar-CH).

^{13}C nmr (CDCl$_3$, 75.47 MHz) 40.5, 40.7, 46.7 (3 x CH$_2$), 55.4 (qC), 76.6, 83.4 (2 x CHOH), 120.5, 123.5, 124.2, 124.3, 124.8, 125.5, 125.5, 125.8, 125.8, 126.3, 126.8, 127.5, 128.4, 128.5, 130.4, (13 x Ar-CH & 1 x C=CH), 141.5, 143.0, 143.1, 144.1, 145.4, 150.2, (5 x Ar-C & 1 x C=CH)

Example 4 Preparation of Compounds III and IV



Compound I (300 mg, 0.8 mmol) was dispersed in ethanol ethyl acetate (9:1, 20 ml) and to this was added sodium borohydride (16 mg, 0.42 mmol). The crude product was extracted into ethyl acetate. Three products were observed by TLC (II, III and IV). The product was isolated by column chromatography eluting with petroleum ether: ethyl acetate (9:1), (Compound III trace amount), (Compound IV, 0.027g, 9%).

Compound III

Low resolution mass Spectrum $C_{26}H_{24}O_2$ requires M^+366, Found M^+366.

^{1}H nmr (δCDCl$_3$, 400MHz) 3.31-3.95 (6H, m, 3 x C<u>H</u>$_2$), 4.17 (1H, s, C<u>H</u>OH), 6.75 (1H, s, C=C<u>H</u>), 7.17-8.05 (13H, m, Ar-C<u>H</u>)

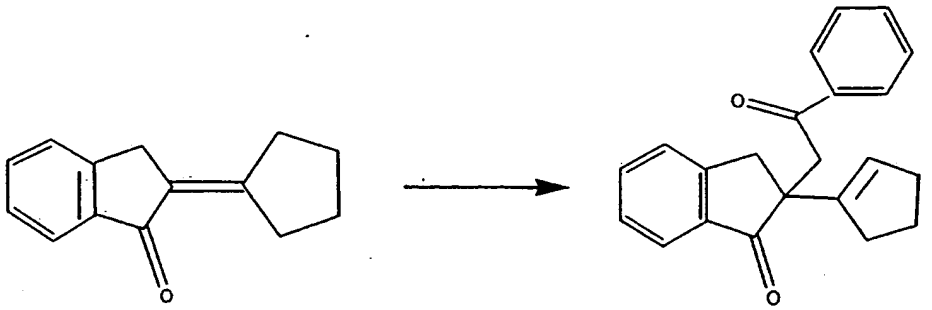
Compound IV

Low resolution mass spectrum $C_{26}H_{24}O_2$ requires M^+366, Found M^+366

^{1}H nmr (δCDCl$_3$, 400 MHz) 3.21 (2H, s, CH_2), 3.56 (2H, d, J=5.8 Hz, CH_2), 3.83 (2H, q, J=17.9Hz, C<u>H</u>$_2$), 5.31 (1H, s, C<u>H</u>OH), 6.49 (1H, s, C=C<u>H</u>), 6.88-8.07 (13H, m, Ar-C<u>H</u>)

^{13}C nmr ($CDCl_3$, 75.47 MHz) 40.2, 43.6, 47.3 (3 x <u>C</u>H$_2$), 53.5 (q<u>C</u>), 82.3 (2 x <u>C</u>HOH), 120.3, 123.3, 124.1, 124.2, 124.3, 126.0, 126.3, 127.1, 128.1, 128.3, 128.9, 133.5 (13 x Ar-<u>C</u>H & 1 x C=<u>C</u>H), 136.7, 139.7, 142.7, 143.4, 143.7, 150.3 (5 x Ar-<u>C</u> & 1 x C=<u>C</u>H), 202.3 (<u>C</u>O)

Example 5 Preparation of Compound V



C V

Compound C (400 mg) was dissolved in clean dry THF (20 ml) at - 78°C, to this was added LDA (0.8 ml) and the mixture was stirred at -78°C for 10 minutes. Phenacyl bromide (1.43 ml. 10 equivs) was added and the solution was allowed to warm to room temperature and stirred for 3 hours under nitrogen.

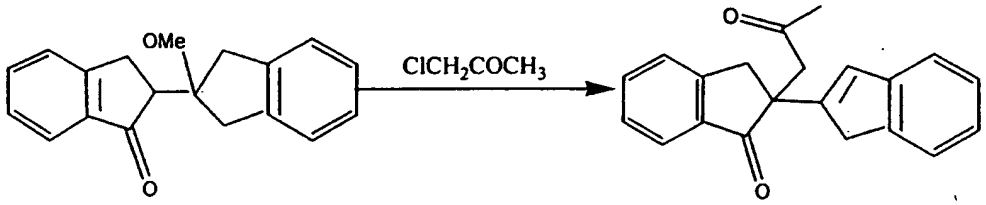
The crude product was extracted into ethyl acetate. The product V was obtained by column chromatography eluting with petroleum ether: ethyl acetate (9:2) (0.12 mg, 7%).

Compound V

Low resolution mass Spectrum $C_{22}H_{20}O_2$ requires M^+316, Found M^+316

^1H nmr ($\delta CDCl_3$, 400 MHz) 1.18-1.84 (6H, m, 3 x CH_2, 3.86-4.26 (4H, m, x CH_2), 7.09-7.94 (10H, m, 1 x C=CH, Ar-CH)

Example 6 Compound VI



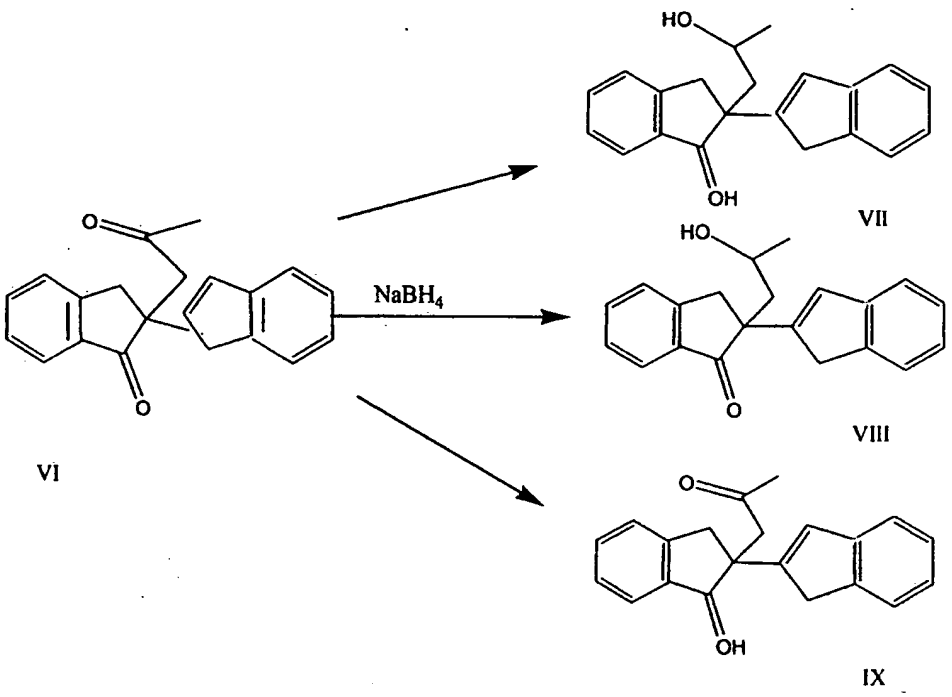
A VI

Compound A (1g, 3.6 mmol) was dispersed in ^{t}BuOH:Et_2O (1:9, 20ml), and to this was added chloropropanone (8 ml). To this solution, which was stirred at room temperature, potassium tert butoxide (1g) in ^{t}BuOH:Et_2O (9:1, 20ml) was added dropwise. The crude reaction mixture was extracted into ethyl acetate. The product VI was isolated by column chromatography eluting with petroleum ether: ethyl acetate (9:1) (0.98g, 75%).

Low resolution mass Spectrum
Requires $C_{21}H_{18}O_2$ M^+302 Found M^+302

^{1}H nmr (δCDCl$_3$, 400 MHz) 2.41 (3H, s, $COCH_3$), 3.21-3.40 (4H, m, 2 x $C\underline{H}_2$), 3.45 (1H, d, J=17.1Hz, C$\underline{H}$ of CH_2), 3.84 (1H, d, J=17.1Hz, C$\underline{H}$ of CH_2), 7.15-7.72 (9H, m, 8 x Ar-C$\underline{H}$ and C=C$\underline{H}$)

Example 7 Compounds VII, VIII and IX



Compound VI (300mg, 0.8 mmol) was dispersed in ethanol/ethyl acetate (9:1, 20 ml) and to this was added sodium borohydride (16mg, 0.42 mmol). The crude product was extracted into ethyl acetate. Three products were observed by TLC (VII, VIII and IX). The products were isolated by column chromatography eluting with petroleum ether: ethyl acetate (9:1), (Compound VII, 73mg), (Compound VIII, 27mg), (Compound IX, 43mg).

Compound VII

^{1}H nmr (δCDCl$_3$, 400 MHz) 2.43 (3H, d, J=8Hz, CHOHC<u>H</u>$_3$), 3.25-3.41 (4H, m, 2 x C<u>H</u>$_2$), 3.47 (1H, m ,C<u>H</u> of CH$_2$), 3.80 (1H, m, C<u>H</u> of CH$_2$), 4.82 (1H, dq, C<u>H</u>OH), 5.01 (1H, s, C<u>H</u>OH), 7.11-7.69 (9H, m, 8 x Ar-C<u>H</u> and C=C<u>H</u>)

Low resolution mass Spectrum

Requires $C_{21}H_{22}O_2$ M^+306 Found M^+306

Compound VIII

^{1}H nmr (δCDC1$_3$, 400 MHz) 2.40 (3H, d, J=8Hz, CHOHC<u>H</u>$_3$), 3.25-3.41 (4H, m, 2 x C<u>H</u>$_2$), 3.45 (1H, m C<u>H</u> of C<u>H</u>$_2$), 3.77 (1H, m, C<u>H</u> of CH$_2$), 4.85 (1H, dq, C<u>H</u>OH), 7.10-7.65 (9H, m, 8 x Ar-C<u>H</u> and C=C<u>H</u>)

Low resolution mass Spectrum

Requires $C_{21}H_{20}O_2$ M^+304 Found M^+304

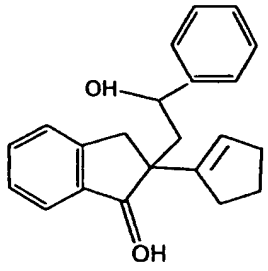
Compound IX

^{1}H nmr (δCDC1$_3$, 400MHz) 2.40 (3H, s, COC<u>H</u>$_3$), 3.23-3.40 (4H, m, 2 x C<u>H</u>$_2$), 3.45 (1H, m, C<u>H</u> of C<u>H</u>$_2$), 3.77 (1H, m ,C<u>H</u> of CH$_2$), 5.03 (1H,s, C<u>H</u>OH), 7.12-7.68 (9H, m, 8 x Ar-C<u>H</u> and C=C<u>H</u>)

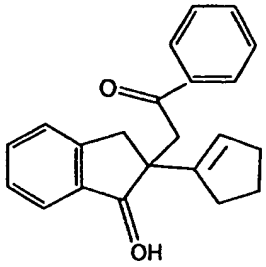
Low resolution mass Spectrum

Requires $C_{21}H_{20}O_2$ M^+304 Found M^+304

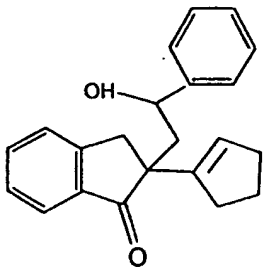
Example 10 Compounds X, XI, XII



X



XI



XII

These compounds are similar to compound V. By virtue of the same chemistry used in the synthesis of compounds II, III and IV the compounds X, XI and XII would be expected. These compounds would be synthesised to a greater yield by a more efficient coupling stage in the formulation of the starting material.

PHARMACOLOGY

Introduction

The indane compounds according to the invention have mast cell stabilising activity and anti-inflammatory activity. The compounds are, therefore, potential anti-asthmatic agents with bronchodilator activity. The mast cell stabilising activity of the compounds suggest their potential use in the treatment of allergic rhinitis, allergic conjunctivitis and other anaphylactic or allergic conditions. The anti-inflammatory activity may have applications in gout, rheumatic diseases, ankylosing spondylistis, polymyalgia rheumatica, temporal arteritis, polyarteritis nodosa, polymyositis and systemic lupus arteriosis and other inflammatory conditions. Topical applications may include: atopic excema, weeping excemas, psoriasis, chronic discoid lupus erythematosus, lichen simplex chronicus, hypertrophic lichen planus, palmar plantar pustulosis. They may also have potential in the treatment of some malignant diseases and as immunosuppressants.

The compounds may also have smooth muscle relaxing activity which may have potential in the treatment of hypertension and peripheral vascular disease, such as intermittent claudication and Reynaud's syndrome, as well as other cardiovascular disorders, such as congestive heart failure, angina pectoris, cerebral vascular disease and pulmonary hypertension. Such compounds are also indicated for potential use in the treatment of certain disorders of the gastro-intestinal tract, such as diverticular disease and irritable bowel syndrome. Similarly, these compounds may have potential as agents for the treatment of disorders of the genito-urinary tract, such as premature labour, incontinence, renal colic and disorders associated with the passage of kidney stones. Member of this group of compounds may also have potential as diuretics analgesics, antipyretics, local anaesthetics, central nervous system depressants and hypoglycaemic agents.

The compounds were assessed for their ability to stabilise mast cell membranes *in vitro*. Mast cells treated with the compounds and un-treated mast cells were stimulated to release histamine. A reduction in histamine release by the treated cells compared to the un-treated cells indicates stabilisation of the membranes.

There follows protocols of each of these assays and a summary of the results.

ABBREVIATIONS

BSS	buffered salt solution
$CaCl_2$	calcium chloride
CO_2	carbon dioxide
DMSO	dimethyl sulphoxide
DSCG	disodium cromoglycate
dH_2O	distilled water
HCl	hydrochloric acid
HEPES	N-2-hydroxyethylpiperazine-N-2-ethanesulphonic acid
KCl	potassium chloride
λem	emission wavelength
λex	excitation wavelength
M	Molar
$MgCl_2$	magnesium chloride
min	minutes
ml	microliters
mM	milli-molar
NaCl	sodium chloride
$NaHCO_3$	sodium hydrogen carbonate
NaH_2Po	sodium hydrogen phosphate
NaOH	sodium hydroxide
O_2	oxygen
oPT	o-phthaldialdehyde
S.E.M.	standard error of mean
w/v	weight per volume
v/v	volume per volume

METHODS

Histamine Release Assay

The buffered salt solution (BSS) was prepared in advance (NaCl 137 mM; KCl 2.7mM; $MgCl_2$ 1.0mM; $CaCl_2$ 0.5mM; NaH_2PO_4 0.4mM; Glucose 5.6mM; HEPES 10 mM). This was dispensed into test tubes and heated to 37°C, each test tube contained 4.5ml BSS. The solvent blank was supplemented with 0.5% (v/v) dimethyl sulphoxide (DMSO) or 0.5% (v/v) distilled water (dH_2O). The two positive controls were supplemented with 0.5% (v/v) DMSO / $2x10^{-5}$M disodium cromoglycate (DSCG) and 0.5% (v/v) DMSO / $2x10^{-5}$ M test compound / 0.5% (v/v) DMSO. The basal release, maximum release and total histamine content incubation tubes contained no additions.

Female Wistar rats (200-300g) were killed in an atmosphere of saturated CO_2. Pre-warmed BSS (10ml) was injected i.p. and the abdomen was massaged for 3 min. The BSS, with suspended mast cells and other cells, was aspirated following a mid-line incision. The aspirate was centrifuged for 5 min at 400g and the supernatent removed. The cells were re-suspended in BSS, at 4°C, and certrifuged as before. The cells were washed in this manner a total of three times. Following the final wash, the pelleted cells were stored at 4°C, for use as soon as possible.

The cells were re-suspended in 7ml BSS. From this, 0.5ml aliquots were transferred to each of the incubation tubes. After 10 min at 37°C, with gentle agitation, Compound 48/80 was added to a final concentration of 2mg/ml, in order to stimulate histamine release. The cell stimulation was stopped after 2 min by the addition of 0.5ml ice cold BSS, the incubation tubes were transferred to an ice bath. The cell suspensions were centrifuged for 5 min at 400g. The "total histamine content" tube was placed at 100°C for 2 min prior to centrifugation. The supernatants were retained for histamine assay.

To 2 ml of supernatent from each tube was added 0.4 ml of 1M NaOH and 0.1ml oPT (1% (w/v) in methanol). This was incubated at room temperature for 4 min. The reaction was stopped by the addition of 0.2 ml of 3M HCl. The supernatant from each incubation tube was assayed in duplicate and run simultaneously with a standard curve in the range 0-1000ng/ml. The presence of the fluorescent product of the reaction was measured using a Shimadzu RF-1501 spectrofluorophotometer set at λex = 360nm, λem = 450nm.

Each drug was tested on at least five animals (n = 5). The results were expressed as a percentage of maximum inhibition of compound 48/80 induced-histamine release in the solvent blank sample. Each drug was compared to DSCG on the same tissues. The basal histamine release in untreated cells was noted, expressed as a percentage of the total histamine content of the cells in suspension.

Mast Cell

Compound	% inhibition of histamine Release (± S.E.M.)	n (number)
II	53.49 ± 2.53	5

Mouse Ear Oedema Model

The mouse ear oedema model was performed using Laca mice (25-35g), of either sex. The animals were sedated with fentanyl/fluanisone (Hypnorm, Janssen). One ear was treated by the topical application of one of a range of test compounds or dexamethasone (all at 300 μg per ear in acetone). After 30 minutes, oedema was induced by the topical application of arachidonic acid (10 μl at 0.4 g/ml in acetone). The width of each ear was measured, both before and 60 minutes after the induction of oedema, using a micrometer screw gauge. Ear oedema was calculated by comparing the ear width before and after induction of oedema and expressed as percentage normal.

Values are expressed as the percentage increase in ear thickness 1 hour after administration of archidonic acid and solvent controls (n=6 except Compound IV, n=4).

Acute Inflammation – Mouse Ear

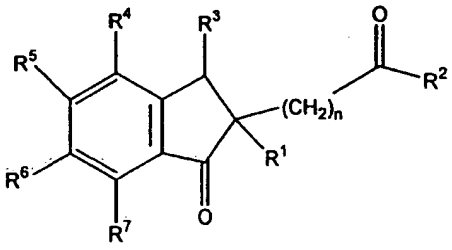
Compound	Mean %	SEM	n (number)
Dexamethasone	41.6	5.6	6
I	49.3	6.7	6
Solvent Control	69.0	5.8	6

Compound	Mean %	SEM	n (number)
Dexamethasone	54.0	6.2	6
II	17.7	5.6	6
III	37.3	6.0	6
IV	13.1	7.4	4
Solvent Control	79.6	12.8	4

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

Claims

1. A compound of any of the formulae 1-4



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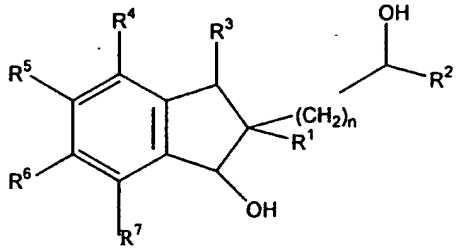

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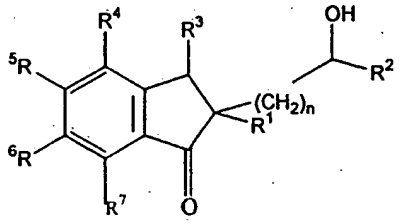

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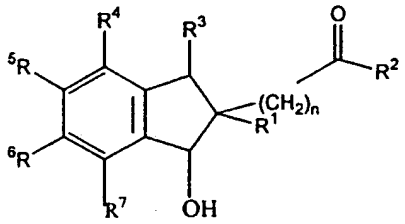

4

wherein R^1 to R^7 are selected from one or more of the same or different of:-

H, halo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, cyclopentyl, alkyl carbonyl, hydro carbonyl, amino, amido, alkylamino, hydroxyamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrazone groups, indane, indene, imide groups, iminoether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitirile, heterocyclic groups containing hetero atoms selected from one or more of N, O or S, aralkyl groups, aryl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenylthiol groups, sulphonic acid groups, sulphoxide groups, sulphone groups, carboxylic acid groups of C_1

to C_{10} which may be substituted or unsubstituted, alkyl, substituted alkyl groups, acyl groups, substituted acyl groups;

where R^1 and R^3 may together represent a double bond and wherein in $(CH_2)_n$, n is 0 to 8.

2. A compound as claimed in claim 1 wherein the compound is on the formula 2 as defined in claim 1.

3. A compound as claimed in claim 1 wherein the compound is of the formula 3 as defined in claim 1.

4. A compound as claimed in any of claims 1 to 3 wherein R^1 to R^7 are selected from one or more of the same or different of:-

hydroxy, alkyl of C_1 to C_{10}, aryl, substituted aryl, cyclopentyl, alkyl carbonyl, hydro carbonyl, amimo, amido, alkalamino, hydroxyamino, amide oxide groups, cyano, indane, indene, oxime, sulphonic acid groups, sulphoxide groups, sulphone groups, or heterocyclic groups containing hetero atoms selected form one or more of N, O.

5. A compound as claimed in any preceding claim wherein R^4 to R^7 are hydrogen.

6. A compound as claimed in any preceding claim wherein R^1 is cyclopentyl.

7. A compound as claimed in claim 6 wherein R^1 is cyclopentenyl.

8. A compound as claimed in any of claims 1 to 5 wherein R^1 is indane.

9. A compound as claimed in any of claims 1 to 5 wherein R^1 is indene.

10. A compound as claimed in any of claims 1 to 6 wherein R^2 is acyl containing 1 to 10 carbon atoms.

11. A compound as claimed in any of claims 1 to 9 wherein R^2 is alkyl containing 1 to 10 carbon atoms.

12. A compound as claimed in claim 11 wherein R^2 is C_1 alkyl.

13. A compound as claimed in any of claims 1 to 9 wherein R^2 is substituted alkyl.

14. A compound as claimed in any of claims 1 to 9 wherein R^2 is aryl having 4 to 8 carbon atoms.

15. A compound as claimed in claim 14 wherein R_2 is C_6 aryl.

16. 1-phenyl-2-((2'-iidenyl)-indan-2-onyl)ethan-1-one.

17. 1-phenyl-2-((2'-iindenyl)-indan-2-ol)ethan-1-ol.

18. 1-phenyl-2-((2'iidenyl)-indan-2-ol)ethan-1-one.

19. 1-phenyl-2-((2'-iidenyl)-indan-2-one)ethan-1-ol.

20. 1-phenyl-2-((2'-cyclopent-1-enyl)indan-1-one)ethan-1-one

21. 1-((2'-iindenyl)-indan-2-one)propan-2-one.

22. 1-((2'-iindenyl)-indan-2-ol)propan-2-ol

23. 1-((2'-iindenyl)-indan-2-one)propan-2-ol

24. 1-((2'-iindenyl)-indan-2-ol)propan-2-one

25. A compound of formula 1 to 4 substantially as hereinbefore described with reference to the examples.

26. A pharmaceutical composition comprising of a compound of any of claims 1 to 25 and a pharmaceutically acceptable carrier.

27. Use of a compound as claimed in any of claims 1 to 25 to achieve mast cell stabilising activity and/or anti-inflammatory activity.

28. Use of a compound as claimed in any of claims 1 to 25 to achieve mast cell stabilising activity.

29. Use of a compound as claimed in any of claims 1 to 25 to achieve anti-inflammatory activity.

30. Use substantially as hereinbefore described with reference to the examples.

31. A compound as claimed in any of claims 1 to 25 to achieve mast cell stabilising activity and/or anti-inflammatory activity.

32. A method of prophylaxis or treatment to achieve mast cell stabilising activity and/or anti-inflammatory activity by administering to a patient an effective amount of a compound as defined any of claims 1 to 25.

33. A process for preparing a compound of any of claims 1 to 25 by reacting 2-(2-(2-methoxyindanyl))-indan-1-one with phenacyl bromide in the presence of potassium tertbutoxide or other suitable base.

34. A process as claimed in claim 33 using alkyl, aryl or acyl halides.

35. A process for preparing a compound of any of claims 1 to 25 by reacting 2-(2'-indanylidene)-indan-1-one LDA in the presence of phenacyl bromide.

36. A process as claimed in claim 35 using alkyl, aryl or acyl halides.

37. A process for preparing a compound of any claims 1 to 25 by reacting 2-(cyclopentanylidene)-indan-1-one with LDA in the presence of alkyl, aryl or acyl halides.

38. A process for preparing compounds of any of claims 1 to 25 in which 2-(2-(2-methoxyindanyl))-indan-1-one is reacted with alkyl, acyl or arylhalides (n=0-8) in the presence of base.

39. A process for preparing a compound of any of claims 1 to 25 by reduction of carbonyl groups using L_iA1H_4 in THF.

40. A process as claimed in claim 39 by selective reduction of carbonyl groups using $NaBH_4$ equivalent.

41. A process as claimed in claim 40 by reduction of carbonyl groups using sodium cyanoborohydride or lithium tritertbutoxide.

42. A process substantially as hereinbefore described with reference to the examples.

INTERNATIONAL SEARCH REPORT

Internat l Application No
PCT/IE 98/00041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C49/683 C07C49/252 C07C49/798 C07C49/747 C07C49/835
C07C35/32 A61K31/12 A61K31/045

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 20802 A (VENANTIUS LIMITED) 12 June 1997 cited in the application see claims	1,4,5,8, 9,11,12, 26-32
X	WO 92 21641 A (PFIZER) 10 December 1992 see claims	1,4,11, 12,14, 15,26
X	US 2 837 571 A (L.H. CONOVER) 3 June 1958 see claims	1,11-13
X	EP 0 183 492 A (FARMOS OY) 4 June 1986 see page 51	1,5,11, 12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1998	07/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonnevalle, E

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INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/IE 98/00041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WACHSEN E ET AL: "Acylgruppenwanderung, V Kinetische Daten der Acylgruppenwanderung von 2-Benzoyl-3-indenyl-acetat und 3-Benzoyl-2-indenyl-acetat" CHEM. BER. (CHBEAM);75; VOL.108 (2); PP.683-92, XP002078463 Univ. Marburg;Inst. Pharm. Chem. Lebensmittelchem.; Marburg; Ger. see page 685 ---	1,5,11, 12,14,15
X	DEHMLOW E V ET AL: "Über die Bildung von Indanonderivaten bei der Pyrolyse von 3-Phenylpropionylchloriden" JUSTUS LIEBIGS ANN. CHEM. (JLACBF,00754617);77; (10); PP.1617-24, XP002078464 Tech. Univ. Berlin;Inst. Org. Chem.; Berlin; Ger. see page 1618 ---	1,5,11, 12
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X	NEGISHI E ET AL: "Carbonylative cyclization via intramolecular trapping of acylmetal derivatives by carbon nucleophiles catalyzed by late transition metals" J. AM. CHEM. SOC. (JACSAT,00027863);89; VOL.111 (20); PP.8018-20, XP002078466 Purdue Univ.;Dep. Chem.; West Lafayette; 47907; IN; USA (US) see page 8019 ---	1,5,11, 12
X	HERMANN K ET AL: "Polymergebundene Cinchonaalkaloide als Katalysatoren in der Michael-Reaktion" HELV. CHIM. ACTA (HCACAV,0018019X);77; VOL.60 (7); PP.2208-12, XP002078467 Univ. Groningen;Dep. Org. Chem.; Groningen; Neth. see page 2210 ---	1,5,11, 12

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INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/IE 98/00041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	GRIGG R ET AL: "Palladium catalyzed cascade carbonylation-cyclization-carbometallat ion-anion capture. Tetramolecular queuing processes" TETRAHEDRON LETT. (TELEAY,00404039);94; VOL.35 (41); PP.7661-4, XP002078468 Leeds Univ.;Sch. Chem.; Leeds; LS2 9JT; UK (GB) see page 7662	1,5,14, 15
X	MEURLING A: "Isolation of the various stereoisomers of 2-benzoyl-2-methyl-1-ind anol and determination of their absolute configurations" CHEM. SCR. (CSRPB9,00042056);87; VOL.27 (3); PP.355-7, XP002078469 Univ. Uppsala;Inst. Chem.; Uppsala; S-751 21; Swed. (SE) see the whole document	1,5,14, 15
A	GB 1 380 089 A (ISTITUTO GENTILIPISA SPA) 8 January 1975 see claims	1,26,27, 29
A	CRAGOE E J, JR. ET AL: "Agents for the treatment of brain edema. 2. '(2,3,9,9a-Tetrahydro-3-oxo-9a-substituted -1H-fluoren-7-yl)oxy!alkan oic acids and some of their analogs" J. MED. CHEM. (JMCMAR,00222623);86; VOL.29 (5); PP.825-41, XP002078470 Merck Sharp and Dohme Res. Lab.;West Point; 19486; PA; USA (US) see page 835	1,6

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. ..tional application No.
PCT/IE 98/00041

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 32
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 32 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/IE 98/00041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0865419 A	23-09-1998
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati· Application No
PCT/IE 98/00041

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